

REMARKS

In this communication, Applicants have amended Claims 1, 3, 5, 8, and 12. No new matter is introduced. Claims 1-20 are pending. Allowance of all elected pending claims is respectfully requested.

Rejections under 35 U.S.C. § 112

Claims 1-13 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reasons stated on pages 3-4 of the Office Action. Applicants respectfully submit that the grounds for the rejection have been obviated by the amendments submitted in this communication. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aebersold et al. (hereinafter Aebersold) in view of Brancia et al. (hereinafter Brancia) for reasons stated on pages 5-7 of the Office Action. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Moreover, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable

expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Independent Claim 1 of the instant application is directed to a method for enhancing identification and relative quantitation of proteins and peptides using mass spectrometry (MS), said method comprising the steps of: reducing disulfide bonds of a first sample from a biological mixture containing proteins and peptides; labeling proteins and peptides in the first sample with a reagent which comprises a thiol-specific reactive group attached to a guanidino group via a linker, said linker can be differentially labeled; separating the proteins and peptides from the sample; digesting the proteins to provide a mixture containing digestion peptides and peptides from the first sample; and subjecting the peptides of (d) to quantitative MS analysis and protein identification. Independent Claim 12 recites all the limitations of Claim 1 and a second labeling step.

Aebersold relates to a method for the quantitative analysis of proteins in mixtures. The method involves selective isolation of peptide fragments with an affinity-labeled protein reactive reagent containing an affinity label, and linker and a thiol-specific reactive group. The Examiner admits that Aebersold fails to teach that the affinity label on the reagent can be a guanidino group but alleges that Brancia teaches the use of guanidination MALDI-MS and that it would have been obvious to one of ordinary skill in the art to combine Aebersold with Brancia. Applicants respectfully disagree.

First of all, the affinity-labeled protein reactive reagent of Aebersold is used to allow selective isolation of the labeled peptides. This function is completely different from the function of the labeling reagent of the instant invention, which provides direct labeling of the peptide for MALDI-MS. The reagent of Aebersold contains an affinity tag which “bind selectively either covalently or non-covalently and with high affinity to a capture reagent.(CR).” (Aebersold, page

11, lines 14-15). The reagent of the claimed invention, on the other hand, contains a guanidino group to enhance the ionization efficiency of the labeled peptides. Aebersold does not teach or suggest using a guanidino group to replace the affinity tag in the affinity-labeled protein reactive reagent. Nor does it provides any motivation or desirability to do so. In fact, the gist of Aebersold is to use the affinity tag to facilitate the isolation of the labeled protein through a capture reagent. Replacing the affinity tag with a guanidino group would completely destroy Aebersold's invention.

Brancia describes that peptides containing an arginine group with a guanidine functionality produce more intense MALDI signals. Brancia specifically teaches a method of converting the lysine residues in peptides to homoarginine residues with O-methylisourea. Brancia, however, does not mention anything about using a guanidino group in a reagent that bind to the peptide through a thiol-specific reactive group and a linker for the purpose of enhancing the ionization efficiency. Accordingly, Applicants respectfully submit that it would not be obvious to one skilled in the art to combine Aebersold and Brancia.

Moreover, even if one skilled in the art were to combine the two references, the reasonable approach would be a to convert the lysine residues on the target peptides to homoarginine (thus increasing the MALDI signals as taught by Brancia) and isolate the converted peptides with the affinity-labeled protein reactive reagent of Aebersold (thus allowing the selective isolation of the peptides as taught by Aebersold). The combination proposed by the Examiner is illogical because it would destroy Aebersold's invention and because Brancia never teach or suggest using a guanidino group on a labeling reagent.

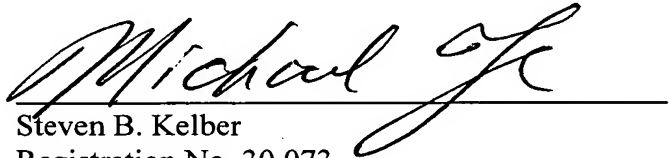
Taken together, Applicants respectfully submit that Aebersold and Brancia, individually or in combination, do not render independent Claims 1 and 12 obvious. Applicants further submit that Claims 2-11 and 13 are patentable because they depend from Claim 1 and define

additional patentable subject matter. Withdrawal of the rejection under 35 U.S.C. § 103(a) to Claims 1-13 is respectfully requested.

In view of the foregoing remarks, favorable reconsideration of all pending claims is requested. Applicants respectfully submit that this application is in condition for allowance and requests that a notice of allowance be issued. Should the Examiner believe that anything further is required to expedite the prosecution of this application or further clarify the issues, the Examiner is requested to contact Applicants' representative at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP


Steven B. Kelber
Registration No. 30,073
Attorney of Record

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085

Michael Ye
Registration No. 47,195

FULL TEXT OF CASES (USPQ2D)

All Other Cases

In re Vaeck (CA FC) 20 USPQ2d 1438 In re Vaeck**U.S. Court of Appeals Federal Circuit
20 USPQ2d 1438****Decided October 21, 1991****No. 91-1120****Headnotes****PATENTS****1. Patentability/Validity - Obviousness - Combining references (§ 115.0905)**

Rejection of claimed subject matter as obvious under 35 USC 103 in view of combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that such person would have reasonable expectation of success; both suggestion and reasonable expectation of success must be founded in prior art, not in applicant's disclosure.

2. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Patent and Trademark Office has failed to establish prima facie obviousness of claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, since prior art does not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill reasonable expectation of success in doing so; expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious expression of unrelated genes in cyanobacteria for unrelated purposes.

3. Patentability/Validity - Specification - Enablement (§ 115.1105)**JUDICIAL PRACTICE AND PROCEDURE****Procedure - Judicial review - Standard of review - Patents (§ 410.4607.09)**

Specification must, in order to be enabling as required by 35 USC 112, first paragraph, teach person skilled in art to make and use invention without "undue experimentation," which does not preclude some experimentation; enablement is question of law which is reviewed independently on appeal, although such determination is based upon underlying factual findings which are reviewed for clear error.

PATENTS**4. Patentability/Validity - Specification - Enablement (§ 115.1105)**

Patent and Trademark Office did not err in rejecting, as non-enabling pursuant to 35 USC 112, first paragraph, claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, in view of relatively incomplete understanding of biology of cyanobacteria as of applicants' filing date, as well as limited disclosure by applicants of particular cyanobacterial genera operative in claimed invention, since there is no reasonable correlation between narrow disclosure in applicants' specification and broad scope of protection sought in claims encompassing gene expression in any and all cyanobacteria.

Case History and Disposition:

Page 1439

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent, serial no. 07/021,405, filed March 4, 1987, by Mark A. Vaeck, Wipa Chungjatupornchai, and Lee McIntosh (hybrid genes incorporating a DNA fragment containing a gene coding for an insecticidal protein, plasmids, transformed cyanobacteria expressing such protein and method for use as a biocontrol agent). From decision rejecting claims 1-48 and 50-52 as unpatentable under 35 USC 103, and rejecting claims 1-48 and 50-51 for lack of enablement, applicants appeal. Affirmed and part and reversed in part; Mayer, J., dissents with opinion.

Attorneys:

Ian C. McLeod, Okemos, Mich., for appellant.

Teddy S. Gron, associate solicitor (Fred E. McKelvey, solicitor and Richard E. Schafer, associate solicitor, with him on brief), for appellee.

Judge:

Before Rich, Archer, and Mayer, circuit judges.

Opinion Text**Opinion By:**

Rich, J.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 USC 103, as well as the rejection of claims 1-48 and 50-51 under 35 USC 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

BACKGROUND**A. The Invention**

The claimed invention is directed to the use of genetic engineering techniques 1 for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus* proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle. As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote 2 kingdom, the

Page 1440

cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within transformed 3 cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

<http://www.bna.com/corp/index.html#V>

More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.

The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:

1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:
(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and
(b) at least one DNA fragment coding for an insecticidally active protein produced by a *Bacillus* strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,
the DNA fragments being linked so that the gene is expressed.

Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers. 5 Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which expresses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

B. Appellants' Disclosure

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus* (*B. thuringiensis*, *B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis*, *Anacystis*, *Synechococcus*, *Agmenellum*, *Aphanocapsa*, *Gloecapsa*, *Nostoc*, *Anabaena* and *Ffremyllia*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis*, linked to (2) a particular promoter, the P_L promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P_L promoter.

C. The Prior Art

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal. The focus of Dzelzkalns, 6 the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT). 7 Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

Sekar I, 8 Sekar II, 9 and Ganesan 10 collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium*, *B. subtilis* and *E. coli*.

Friedberg 11 discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O_LP_L operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis,

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis*"

Miller 12 compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases 13 purified from two different species of cyanobacteria (*Freymyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli*. Nierzwicki-Bauer 14 identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbc L*, the large subunit of the enzyme ribulose-1, 5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.

Chauvat 15 discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

Reiss 16 studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

Kolowsky 17 discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium. Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

D. The Grounds of Rejection

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 USC 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus*, and the advantages of expressing such genes in heterologous 18 hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the

Page 1442

expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was *prima facie* obvious.

Additional rejections were entered against various groups of dependent claims which we need not address here.

All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above.

The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 USC 112, first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) 19 and (z) 20 as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided in the specification. With respect to unpredictability, the examiner stated that the cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis*, *Anacystis*, *Synechococcus*, *Agmenellum*, *Nostoc*, *Anabaena*, etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera. Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)."

OPINION

A. Obviousness

We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 USC 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff*, 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990).

[1] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

Page 1443

[2] We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

<http://www.bna.com/corp/index.html#V>

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli*. While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed *bacterial* hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae. 21 Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell*, this court affirmed an obviousness rejection of a claim to a method for

Page 1444

producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 USPQ2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 USPQ2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

<http://www.bna.com/corp/index.html#V>

a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.

....
... Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 USPQ2d at 1679-80.

In contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. Enablement

[3] The first paragraph of 35 USC 112 requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 USPQ2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 USPQ2d at 1402.

In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

[4] Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification).

Page 1445

22 Accordingly, we affirm the § 112 rejection as to those claims.

In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It

is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. *See Fisher*, 427 F.2d at 839, 166 USPQ at 24. In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.

Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera *Anacystis* and *Synechocystis*. Claim 48, which depend from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria. Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

CONCLUSION

The rejection of claims 1-48 and 50-52 under 35 USC 103 is *reversed*. The rejection of claims 1-46 and 50-51 under 35 USC 112, first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed*.
AFFIRMED-IN-PART, REVERSED-IN-PART

Footnotes

Footnote 1. Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell*, 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988), and are not repeated here.

Footnote 2. All living cells can be classified into one of two broad groups, procaryotes and eucaryotes. The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus wherein their DNA resides.

Footnote 3. "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part of the host cyanobacteria, to be replicated as new cyanobacteria are generated.

Footnote 4. "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of DNA) via messenger RNA to ribosomes where a specific protein is made.

Footnote 5. In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.

Footnote 6. *Nucleic Acids Res.* 8917 (1984).

Footnote 7. Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.

Footnote 8. *Biochem. and Biophys. Res. Comm.* 748 (1986).

Footnote 9. *Gene* 151 (1985).

Footnote 10. *Mol. Gen. Genet.* 181 (1983).

Footnote 11. *Mol. Gen. Genet.* 505 (1986).

Footnote 12. *J. Bacteriology* 246 (1979).

Footnote 13. RNA polymerase, the enzyme responsible for making RNA from DNA, binds at specific nucleotide sequences (promoters) in front of genes in DNA, and then moves through the gene making an RNA molecule that includes the information contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.

Footnote 14. *Proc. Natl. Acad. Sci. USA* 5961 (1984).

Footnote 15. *Mol. Gen. Genet.* 185 (1986).

Footnote 16. *Gene* 211 (1984).

Footnote 17. *Gene* 289 (1984).

Footnote 18. Denotes different species or organism.

Footnote 19. MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:

In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure....

Footnote 20. MPEP 796.03(z), "Undue Breadth," provides in part:

n applications directed to intentions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol*, 1938 C.D. 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...

Footnote 21. *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Prokaryotae"). Prokaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom; Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).

Footnote 22. The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan*, 559 F.2d 595, 605-07, 194 USPQ 527, 536-38 (CCPA 1977). See also *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251, 9 USPQ2d 1461, 1464 (Fed. Cir. 1989) (citing *Hogan*); *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1568-69, 15 USPQ2d 1039, 1047-48 (Fed. Cir. 1990) (directing district court, on remand, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of *Fisher*), *cert. dismissed*, — U.S. —, 111 S. Ct. 1434 (1991). We therefore do not consider the effect of *Hogan* and its progeny on *Fisher*'s analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher*, 427 F.2d at 839, 166 USPQ at 24.

Footnote 23. The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

Dissenting Opinion Text

Dissent By:

Mayer, J., dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co.*,

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

<http://www.bna.com/corp/index.html#V>

832 F.2d 581, 584, 4 USPQ2d 1621, 1624 (Fed. Cir. 1987); *Eaton Corp. v. Appliance Valves Corp.*, 790 F.2d 874, 877, 229 USPQ 668, 671 (Fed. Cir. 1986). But that is precisely what the court has permitted here. The PTO conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if thought this opinion were more persuasive than the board's, I could not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966); *Jurgens v. McKasy*, 927 F.2d 1552, 1560, 18 USPQ2d 1031, 1037 (Fed. Cir. 1991). And "[w]here there are two permissible views of

Page 1446

the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City*, 470 U.S. 564, 574 (1985). The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff*, 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990); *In re Kulling*, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1057 (Fed. Cir. 1990). There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.

- End of Case -

Hodosh v. Block Drug Co., Inc.

(CA FC)

229 USPQ 182

Decided March 24, 1986

No. 85-2607

U.S. Court of Appeals Federal Circuit

Headnotes

PATENTS

1. Patentability -- Invention -- Specific cases -- Chemical (§ 51.5093)

Summary judgment holding that claimed tooth desensitizer was invalid for obviousness was improper, in view of existing questions of material fact concerning various terms used in Chinese and European references.

2. Patentability -- Invention -- In general (§ 51.501)

Secondary considerations and additional evidence likely to be considered at trial must be considered in obviousness determination.

Particular patents -- Dental Treatments

3,863,006, Hodosh, Method for Desensitizing Teeth, holding of invalidity reversed.

Case History and Disposition:

Page 182

Appeal from District Court for the District of New Jersey, Sarokin, J.; 226 USPQ 645 .

Action by Milton Hodosh, and Richardson-Vicks, Inc., against Block Drug Company, Inc., and Dentco, Inc., for patent infringement. From summary judgment for defendants, plaintiffs appeal. Reversed and remanded.

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

<http://www.bna.com/corp/index.html#V>

Attorneys:

John O. Tramontine, and Fish & Neave, and Hugh A. Chapin, and Kenyon & Kenyon, all of New York, N.Y. (W. Edward Bailey, Norman H. Beamer, Fish & Neave, Paul Lempel, William J. McNichol, and Kenyon & Kenyon, all of New York, N.Y., on the brief) for appellants.

Jerome G. Lee, and Morgan, Finnegan, Pine, Foley & Lee, both of New York, N.Y. (William S. Feiler, Maria C.H. Lin, Morgan, Finnegan, Pine, Foley & Lee, Marvin C. Soffen, Edward A. Meilman, and Ostrolenk, Faber, Gerb & Soffen, all of New York, N.Y., on the brief) for appellees.

Judge:

Before Rich, Davis, and Baldwin, Circuit Judges.

Opinion Text**Opinion By:**

Rich, Circuit Judge.

This appeal is from the July 12, 1985, judgment of the United States District Court for the District of New Jersey, 226 USPQ 645, granting summary judgment to Block Drug Company, Inc., et al. (Block) and holding that all six claims of patent No. 3,863,006 for "Method of Desensitizing Teeth" ('006 patent), issued to Dr. Milton Hodosh and licensed to Richardson-Vicks, Inc. (collectively, Hodosh), are invalid for obviousness under 35 USC 103. We reverse remand.

Background

Tooth desensitizers reduce discomfort and pain caused by tooth hypersensitivity or exposed dentin, the portion of the tooth between the enamel and the pulp which includes a myriad of microscopic tubules. Persons suffering from this condition react painfully to hot or cold foods, citric acid or sweets, or everyday chemical, thermal, or tactile stimuli including toothbrush contact.

Milton Hodosh, a practicing dentist for about thirty years, independently developed the claimed subject matter of the '006 patent and granted Richardson-Vicks an exclusive license to make, use, and sell the claimed invention; the latter markets its tooth desensitizing toothpaste under the trademark "Denquel."

Claim 1 of the '006 patent¹ reads:

The method of desensitizing hypersensitive dentin and cementum by applying thereto an agent the essential ingredient of which is a nitrate of one of the following alkali metals: potassium, lithium or sodium said nitrate comprising between 1 percent and 20 percent by weight of said agent.

The remaining claims appear in the opinion below.

Appellee Block has, since 1961, marketed a tooth desensitizing toothpaste, covered by its patent No. 2,122,483 (the Rosenthal patent) for "Strontium Ion Toothpaste" issued in 1964, under the trademark "Sensodyne." The Rosenthal patent and the '006 patent disclose toothpaste formulae which are the same except that the latter contains, as a desensitizing agent, potassium nitrate instead of the Rosenthal-Block strontium chloride. After requesting and being denied a license under the '006 patent, Block developed its own potassium nitrate-containing tooth-desensitizing toothpaste called "Promise" and "Sensodyne-F."²

March 30, 1983, Hodosh sued Block alleging that the sale of "Promise" and "Sensodyne-F" contributorily infringed and actively induced infringement of the '006 patent. Block answered and counterclaimed alleging patent misuse and consequent unenforceability of the '006 patent. On July 11, 1984, Block moved for summary judgment as to both misuse and patent invalidity. Oral argument was heard October 16, 1984, and decision was reserved. June 14, 1985, the reported decision was handed down granting the motion as to patent invalidity and dismissing the motion on misuse as moot, resulting in the judgment now on appeal.

The district court heard no expert testimony, but did hear arguments of counsel, receive briefs, review exhibits, and had before it declarations and affidavits from experts on both sides commenting on the eight prior art references involved here, including the Rosenthal patent. The court determined that there were no genuine issues of material fact and concluded as a matter of law that the claims of the '006 patent were invalid under §103 because the Rosenthal patent disclosed each element claimed in the '006 patent except the potassium nitrate, which, in its view, was disclosed in two Chinese references, both based on ancient Chinese writings. The court also stated that six European references supported its conclusion of obviousness.

Because the appropriateness of summary judgment is determined on an analysis of the facts, *First National Bank of Arizona v. Cities Service Co.*, 391 U.S. 253 (1968), and because everything about these references, as a whole, see, e.g., *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547-48 (Fed. Cir. 1985), is important to our determination, we review the record and lay out the relevant portions of the references in some detail.

A. The Chinese References

1. The Grand Dictionary of Chinese Medicine and Drugs (The Grand Dictionary)

The *Grand Dictionary*, published in Hong Kong in 1963 and written in Chinese, is based on ancient Chinese compilations assembled roughly 500 years ago from works of physicians going back 4000-5000 years. Only a portion of the 1963 Chinese text was before the court and is before us on appeal. For purposes of this litigation, that portion was translated into English by Block's translator, Roger Wei-Ming Tsao (Mr. Cao). Mr. Cao is a doctor of Chinese medicine and a bilingual tutor. Block's other expert, Dr. Stephen Wei, a professor of dentistry fluent in Chinese, concurred in that translation. The writings from which the *Grand Dictionary* was compiled are not in evidence nor are any earlier writings.

In a nutshell, the district court relied upon the *Grand Dictionary* because of its discussion of "xiao shi" to which the Grand Dictionary associates the name "niter" and the chemical composition KNO₃ and the ability to cure, inter alia, tooth pain. The court's opinion was that this reference teaches the use of xiao shi, which is the same as niter and is therefore the same as potassium nitrate, to cure tooth pain; thus, the teachings of the Rosenthal patent and the *Grand Dictionary* show that the '006 invention would have been obvious.

The following discussion and quotations are part of an attempt to convey the nature of the *Grand Dictionary*. The translated portion of the *Grand Dictionary* is entitled "Niter." The text under the first subheading "Nomenclature" reads: "It was so named because it has the power to consume various stones." Under "Other Names Stated in Classical Medical Books," the text reads "Mang Xiao (Bie-Lu), Bitter Xiao (Zhen-Quan), Flaming Xiao (Tu-Su) . . . and Xiao-Shi" Thereafter, following "Foreign Names," the *Grand Dictionary* reads: "Salpetrae, Salnitri (in Latin); Niter (in English); and Salpoter (in German)." One page later, "KNO₃" is listed under "Chemical Composition."

The portion upon which Block and the district court rely to show that this substance cures tooth pain is headed "Collective Statements" and reads:

(Ming): Li-Shi-Zhen said: It cures summer infections and the catching of colds. It cures acute enteritis with severe vomiting, exertion through excessive sexual activity, black jaundice, chronic abdominal pain, conjunctivitis, headaches and tooth pain.

The next three or so pages of the *Grand Dictionary* list the ailments that this substance cures. An interesting but not atypical paragraph reads: "For curing the paralysis of the four limbs, leprosy or problems caused by Taoist stone eating." This substance also apparently cures indigestion, lack of energy, typhoid, cataracts, and much, much more. The *Grand Dictionary* compares what appears to

Page 184

be various forms in which xiao shi is found, and the characteristics of each. An excerpt is:

Pu-Xiao (Na_2SO_4) has the nature of water, tastes salty, and its flavor is cold. It can only descend and cannot ascend. It is Yin within Yin -- that's why it can cleanse the accumulation in the gastrointestinal tract and can expel the San-Jiao devilish fire. Whereas Niter (KNO_3) has the nature of fire, tastes bitter and spicy, tastes slightly salty and has a flavor which is very warm, it's [sic] nature is ascending. It is fire within water. That's why it can break the accumulation and disperse hardness, and cure the febrile diseases.

2. Ben Cao Gang Mu

Ben Cao Gang Mu (*Ben Cao*) is a treatise on Chinese Medicine published in Hong Kong, in Chinese, in 1930, 1954, and 1965, but was originally written by Li-Shi-Zhen who lived during the Ming Dynasty.³ Like the *Grand Dictionary*, only a portion of the Chinese text *Ben Cao* is in evidence and that portion was translated by Mr. Cao and Dr. Wei for purposes of this litigation. The district court relied upon *Ben Cao* because it discusses "xiao shi," which the translation of *Ben Cao* states is "niter" and associates the ability to cure "tooth pain (Ya Tong or Ya Teng)."

It is important to note, and the district court appeared to accept as fact, that the portion of the *Grand Dictionary* relied upon was compiled during the Ming Dynasty of the 13th to 15th centuries in *Ben Cao Gang Mu* so that the relevant portion of the *Grand Dictionary* is substantially a restatement of *Ben Cao* with some modification by an unidentified author. The court stated that these two references "quote the same Ming Dynasty source as labeling KNO_3 for tooth pain."

The *Ben Cao* translation is entitled "Xiao-Shi (Niter)" and refers to the same "Other names" for this substance listed in the *Grand Dictionary*. With respect to the quoted sections above, the *Ben Cao* translation is nearly verbatim. It has this to say about tooth pain:

Da Ming states: It cures summer infections and the catching of colds, acute enteritis with severe vomiting, exertion thru excessive sexual activity and black jaundice, chronic abdominal pain, conjunctivitis, headache and tooth pain (Ya-Tong or Ya Teng).

Hodosh argues that summary judgment was inappropriate; issues of fact as to the meanings of xiao shi and ya tong remain because a skilled dental researcher would surely seek and obtain a complete translation of the *Grand Dictionary* and of the other ancient Chinese references and would read those references carefully. Hodosh also argues that the ancient references should be dismissed because a person skilled in the art would find them incredible and would regard them as a quagmire of medical and dental nonsense. It therefore takes issue with the court's holding quoted below which apparently precluded inquiry into the accuracy of the references by one skilled in the art:

[A]ttacks upon the translation leading up to the prior art reference embodied in the *Grand Dictionary of Chinese Medicine and Drugs*, . . . or upon Chinese medicine as a whole, . . . are not here regarded as particularly pertinent, since they require skill beyond the scope of the "experienced researcher in dental fields"

Hodosh relies heavily on its expert's, Dr. Shklar's, testimony about the Chinese references: "[T]hey represent in

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

modern terms, materials that are rarely comprehensible and frequently contradictory in their literal terms. The materials are largely seen by contemporary medical scientists as absurd; no serious medical researcher would waste his or her time with them." ⁴ Hodosh also contests this holding by the district court:

Nor, if it is true that KNO₃ alleviates tooth sensitivity, is such reference in the prior art rebutted by the existence of errors in the reference such as, for example, the claim that KNO₃ is a cure for "exertion through excessive sexual activity." Whatever the merits of the other aspects of the Chinese references, the fact that they reveal KNO₃ to be a cure for ya tong is what is dispositive here. The reference clearly discloses such function of potassium nitrate, albeit in the context of otherwise incredible, and even erroneous descriptions of the compound's quality.

With respect to the specific meaning of xiao shi as used in these references, both Dr. Shklar and Hodosh's other expert, Mr. Yen, a professional translator of Chinese and English lan

Page 185

guages, stated that the compiler of the *Grand Dictionary* erred in associating potassium nitrate or niter with xiao shi. Mr. Yen states that he

was not able to render one single precise version because various dictionaries contain different and even conflicting definitions. For example, *Source of Words*, a Chinese language dictionary, published by Commercial Press, Taiwan, which has editions dating back to 1915, defines "Xiao-Shi" as "Mang-Xiao" on page 1255, and under "Mang-Xiao" on page 1770, reference is made that "Mang-Xiao" is "Liu-Suen-Na," and on page 1523 "Liu-Suen-Na" is defined as sodium sulfate (Na₂SO₄ · 10H₂O).

Mr. Yen also stated that "Xiao-Shi could be more than one material and that more than one material may be represented by the term 'Xiao-Shi'."

Dr. Shklar concurred:

In my opinion, therefore, the answer to the question: What was "Xiao-Shi," is that it represented many different materials which cannot be identified with certainty.

Thus, these Exhibits did not describe potassium nitrate to one skilled in the art any more than any of the hundreds of salts, ores and oxides that possess some of the enumerated properties.

In addition, Dr. Shklar stated: "It is insufficient to simply state, as the Block translator does, that 'Xiao-Shi' is 'niter,' and then cite a modern dictionary to 'establish' that 'niter' is potassium nitrate." With respect to both the *Grand Dictionary* and *Ben Cao*, he stated that "the translator appears to have inserted the term 'niter' into the text where the phrase 'consumer of stones' actually belongs."

Block's arguments, on the other hand, in part based on the short affidavit by Mr. Wei, substantially follow the district court's opinion. Block also challenges the competence of Hodosh's experts stating that they "either had no knowledge or training in the Chinese language or Chinese medicine or were unfamiliar with dentistry or medicine generally." Block also emphasizes that the Chinese references correctly disclose many of potassium nitrate's characteristics, like burning with a violet flame, useability for making signal fires and gun powder, and its water solubility; these three properties of xiao shi in the Chinese references definitely confirm, according to Block, that xiao shi is potassium nitrate, KNO₃.

B. The European Prior Art

This art is contained in six references and was not relied upon to any significant degree by Block or the district court. Hodosh scarcely mentions it on appeal, instead preferring to show the existence of genuine issues of material fact with respect to the Chinese references. After concluding that using potassium nitrate to cure tooth pain would have been obvious from Rosenthal in view of the Chinese art, the court stated: "Such holding is strengthened by the European prior art which, while ambiguous because of the several conflicting definitions in the

term 'niter,' at least suggest to one skilled in the art that potassium nitrate ought to be tried as a cure for tooth pain in general."

Block submitted no affidavits that addressed the substance of the European references. Hodosh's Dr. Shklar, on the other hand, stated why this art, part of the "humors, spirits and Alchemy of the Dark Ages" having whatever medicinal effect they did by virtue of their use of wine, opium, or other narcotic substances, would have been questioned by one skilled in the art. He specifically contends that Block's translation of "nitre" is erroneous: "it is common knowledge that these terms meant sodium carbonate and/or sodium carbonate-sodium bicarbonate mixture. . . ."

To afford a glimpse of the nature of these references, an interesting and typical excerpt, one quoted by the district court, based upon a statement by the long since deceased French surgeon Guy de Chauliac reads that "a mixture of 'cuttlebone, small white sea shells, pumice, burnt stag's horn, *nitre*, alum, rock salt, burnt roots of iris, aristolochia, and reeds' could create an effective dentifrice." (District court's emphasis.) Three of the European references are based on that statement. The district court noted the others:

Additionally, a 1693 treatise by the British Professor of Physics William Salmon states that nitrum "held in the Mouth . . . immediately helps the Toothach, if burnt and used in a Dentifrice, it cleanses and whitens the Teeth." . . . Similarly, a reference work by Hardianus a Mynsicht, translated into English in 1682, describes a mixture, including "nitre" as a "tincture for the toothache." . . . Finally, Pliny the Elder, in his *Historie of the World, The Second Tome*, translated into English in 1601, describes the use of nitre to "easeth the toothach, if the mouth and gums be washed therewith," or if burned, as a dentifrice. [Reference to Exhibits omitted.]

With this description of both the Chinese and European references, and of what they represent as a whole, in hand, we consider the proper application of the *Graham* standards and their effect upon the propriety of summary judgment in this case. See generally *Graham v. John Deere Co.*, 383 U.S. 1, 17 [148 USPQ 459, 467] (1966); *Panduit Corp. v. Dennison*

Page 186

Manufacturing Co., 774 F.2d 1082, 227 USPQ 337 (Fed. Cir. 1985).

OPINION

A. Summary Judgment

Summary judgment, in patent as in other cases, is appropriate where there is no genuine issue of material fact, and the movant is entitled to judgment as a matter of law. See *Molinaro v. Fannon/Courier Corp.* 745 F.2d 651, 653-54, 223 USPQ 706, 707 (Fed. Cir. 1984). The movant bears the burden of demonstrating the absence of all genuine issues of material fact, and the district court must view the evidence in a light most favorable to the nonmoving party and draw all reasonable inferences in its favor. See *United States v. Diebold, Inc.*, 369 U.S. 654, 655 (1962); *Palumbo v. Don-Joy Co.*, 762 F.2d 969, 973, 226 USPQ 5, 7 (Fed. Cir. 1985). The party opposing summary judgment must show an evidentiary conflict on the record; mere denials or conclusory statements are not sufficient. *Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd.*, 731 F.2d 831, 836, 221 USPQ 561, 564 (Fed. Cir. 1984). Summary judgment is authorized where it is quite clear what the truth is. *Sartor v. Arkansas Natural Gas Corp.*, 321 U.S. 620, 627 (1944).

B. The Issues Below

The decision and opinion of the district court granting summary judgment dealt with two issues: the first was whether the '006 patent is invalid as anticipated under §102(b), the court holding it is not; and the second was whether the '006 patent is invalid for obviousness under §103, the court holding that it is. Hodosh of course appeals the summary judgment with respect to only the issue on which it lost -- obviousness and Block has not appealed. Because we are remanding for trial, however, we will comment briefly on anticipation to make it clear

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

<http://www.bna.com/corp/index.html#V>

that we deem that question to have been conclusively disposed of in this case and because it is closely related to the obviousness issue.

1. Anticipation, §102(b)

We agree entirely with the district court's holding that the '006 patent is not invalid as anticipated because there is no issue of fact that none of the prior art references discloses every element of the claimed invention. This issue was, therefore, appropriately and properly disposed of by summary judgment.

We do not agree, however, with some of the district court's remarks about anticipation, in particular, that the unavailability of the Chinese references and whether one skilled in the art could locate them with "reasonable diligence" bears on whether those references anticipate the claimed subject matter. Whether a reference is available as prior art and whether it anticipates (i.e., contains every claimed element) are separate questions. Moreover, the district court's determination that the references are unavailable for §102 purposes seems to be inconsistent with the approach subsequently taken by the district court in determining obviousness. The court later used these same references to support its holding that the claimed subject matter would have been obvious at the time the invention was made to one of ordinary skill in the art.

2. Obviousness, §103

[1] Questions of material fact remain with respect to the meaning of various terms used in the Chinese and European references and we therefore hold that summary judgment on the ground of obviousness of the claimed invention was improper.

The district court's statement that ya tong means tooth hypersensitivity as well as tooth pain is the resolution of a head-on factual controversy. The court improperly drew the inference against Hodosh, the nonmoving party, that a statement about ya tong made to the German Patent Office by Dr. Hodosh's German patent agent was made with knowledge of the Chinese references. The statement in question occurred seven years after the '006 patent issued in connection with Dr. Hodosh's counterpart German application. The statement was: "The supersensitivity of dentine has been known for a long time and can be traced back 4000 years to the Chinese where it was known as 'Ya Tong'." Hodosh in this suit disclaims this statement urging that it was factual error.

There is no evidence that the above statement was based on the Chinese references or that Dr. Hodosh conveyed this information to the German patent agent. The important fact question as to the meaning of ya tong cannot be overcome simply by styling this statement an admission binding on Hodosh. Hodosh is entitled, as Block essentially concedes, to rebut the statement with evidence to the contrary. Hodosh will have that chance at trial.

Nor does the statement in the affidavit of Block's expert, Dr. Wei, that ya tong means tooth hypersensitivity eliminate the presence of the question of the meaning of ya tong. As the Supreme Court long ago observed, "Ex

Page 187

perience has shown that opposite opinions of persons professing to be experts, may be obtained to any amount. . . ." *Winans v. New York and Erie Railroad Co.*, 62 U.S. 88 (1859). The substance of Dr. Sklhar's affidavit on behalf of Hodosh goes far beyond merely denying that ya tong means tooth hypersensitivity and thus is more than adequate to show an evidentiary conflict on the record with respect to this crucial point, thus precluding summary judgment. *Cf. Union Carbide Corp. v. American Can Co.*, 724 F.2d 1567, 1571, 220 USPQ 584, 587-88 (Fed. Cir. 1984).

Furthermore, a genuine issue of material fact exists with respect to the meaning of the terms nitre, nitrum, and nitri as used in the European references. Dr. Sklhar's affidavit is more than adequate to withstand the challenge of this summary judgment motion. A reasonable inference that these terms are sodium, as opposed to potassium, compounds is permissible; Hodosh has shown an evidentiary conflict on the record. The European references, Dr. Sklhar explained in his affidavit, are based on the 77 A.D. writings of Pliny The Elder, who understood these terms

Copyright 2004, The Bureau of National Affairs, Inc. Reproduction or redistribution, in whole or in part, and in any form, without express written permission, is prohibited except as permitted by the BNA Copyright Policy.

<http://www.bna.com/corp/index.html#V>

to mean "sodium carbonate and/or a sodium carbonate-sodium bicarbonate mixture."

The obviousness determination here, given the existence of genuine material issues of fact with respect to the meanings of terms used in these references, is not suitably disposed of by summary judgment under the rules pertaining thereto. *See generally Palumbo*, supra, and *Lemelson v. TRW, Inc.*, 760 F.2d 1254, 1260-61, 225 USPQ 697, 700-01 (Fed. Cir. 1985). The fact issues herein must be resolved by trial in which the conflicting views of the experts will be subject to the refining fire of cross examination, a more effective means of arriving at the legal conclusion of obviousness vel non than perusal of ex parte affidavits and declarations of partisan experts lobbed at each other from opposing trenches.

We observe, for the benefit of the trial court, that we are totally unimpressed by Block's forensic device of comparing the Rosenthal prior art toothpaste formula and the Hodosh toothpaste example in parallel columns and then asserting, as though it were filled with significant meaning, that the "only difference is the use of potassium nitrate in place of strontium chloride," or that "the Hodosh patent merely substitutes potassium nitrate for strontium chloride." This device was pushed to the limit in oral argument by pointing out that the Hodosh toothpaste has the *same* formula, *except* for the active desensitizing ingredient, down to the last decimal point. This argument is meaningless on the obviousness issue. "Sensodyne" and apparently other desensitizing toothpaste formulae being well known as commercial products, it is entirely clear that Dr. Hodosh's invention was the discovery of an apparently superior *desensitizing agent* and he never thought it was a toothpaste formula. He made that invention even if it should later be decided that it was known to the Chinese. It is apparent that Hodosh's patent solicitor merely adopted the prior art Rosenthal toothpaste base formula as a convenient example to illustrate the kind of a paste in which the Hodosh desensitizer might be used, which was within his right. The similarities -- indeed, identity -- of the paste bases is irrelevant in considering the issue of the unobviousness of the desensitizer. The Rosenthal patent, cited as prior art by Hodosh in his patent specification, was the jumping-off place for the description of his discovery. Hodosh does not claim to have been the first inventor of a desensitizing toothpaste; he claims to have improved it. The issue for trial is whether his improvement would have been obvious. ⁵

C. Secondary Considerations

The district court refused on the motion for summary judgment to consider the evidence of secondary considerations. After acknowledging its existence and the arguments based on it, it stated:

Page 188

However, the court continues to find that the Hodosh patent is invalid on grounds of obviousness; these secondary considerations stem not from the novelty or inventiveness engendered by substituting potassium nitrate in an already existing formula, but from a lack of knowledge on the part of those in the field of the references here cited. That lack is here overcome by the presumption of omniscience discussed, *supra*, a rule of law by which the court is bound, whatever its merits.

[2] That secondary considerations are not considered unless there is evidence that those in the industry knew of the prior art is a non sequitur. Evidence of secondary considerations is considered independently of what any real person *knows* about the prior art. These considerations are *objective* criteria of obviousness that help illuminate the subjective determination involved in the hypothesis used to draw the legal conclusion of obviousness based upon the first three factual inquiries delineated in *Graham*. Thus, to require that actual inventors in the field have the omniscience of the hypothetical person in the art is not only contrary to case law, *see Kimberly-Clark v. Johnson & Johnson*, 745 F.2d 1437, 223 USPQ 603 (Fed. Cir. 1984), but eliminates a useful tool for trial judges faced with a nonobviousness determination.

The secondary consideration evidence of record and the additional evidence likely to be submitted at trial must be considered in the obviousness determination. *See generally Fromson v. Advance Offset Plate, Inc.*, 755 F.2d

1549, 1557, 225 USPQ 26, 32 (Fed. Cir. 1985).

Conclusion

The grant of summary judgment of invalidity is *reversed* and the case is *remanded* for trial in accordance with this opinion.

REVERSED AND REMANDED

Footnotes

Footnote 1. A certificate of reexamination confirming the patentability of claims 1-6 of the '006 patent was issued June 21, 1983, as a result of Hodosh's request for reexamination in 1982. Only one of the prior art references involved here, the Rosenthal patent, *infra*, was considered in the reexamination.

Footnote 2. Block also initiated regulatory proceedings designed to delay or prevent Richardson-Vicks' marketing of "Denquel." Block, having allegedly failed to comply with Food and Drug Administration (FDA) procedures before marketing "Promise" and "Sensodyne-F" in competitive response to Richardson-Vicks' introduction of "Denquel," is currently defending itself in forfeiture proceedings initiated by the FDA.

Footnote 3. The Ming Dynasty (1368-1644 AD) was marked by the restoration of traditional institutions in China and the development of the arts, especially in porcelain, textiles, and painting.

Footnote 4. Dr. Shklar is the Charles A. Brackett Professor of Oral Pathology at the Harvard School of Dental Medicine, and is an acclaimed expert in dentistry. He is also an expert on the history of dentistry and holds membership in the American Academy of the History of Dentistry.

Footnote 5. Our comments on the district court's obviousness determination generally include the following tenets of patent law that must be adhered to when applying §103: (1) the claimed invention must be considered as a whole (35 USC 103; *see, e.g., Jones v. Hardy*, 727 F.2d 1524, 1529, 220 USPQ 1021, 1024 (Fed. Cir. 1984) (though the difference between claimed invention and prior art may seem slight, it may also have been the key to advancement of the art)); (2) the references must be considered as a whole and suggest the desirability and thus the obviousness of making the combination (*see, e.g., Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)); (3) the references must be viewed without the benefit of hindsight vision afforded by the claimed invention (*e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983)); (4) "ought to be tried" is not the standard with which obviousness is determined (*Jones, supra*, 727 F.2d at 1530, 220 USPQ at 1026); and (5) the presumption of validity remains constant and intact throughout litigation (35 USC 285; *e.g., American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359-60, 220 USPQ 763, 770 (Fed. Cir. 1984)).

- End of Case -

